REMARKS

Amendments to the claims

In the Office Action mailed January 22, 2009, claims 18-20 and 33-38 stand rejected. Claim 18 has been amended and new claim 39 has been added with the present submission. As such, claims 18-20 and 33-39 are under consideration.

Claim 18, part (c) has been amended back to the language presented in the claims that were introduced into prosecution in a response filed on June 21, 2005, which simply recites "the sense strand includes a terminal cap moiety at its 5'- and 3'-ends." A new part (d) has been added to claim 18, which recites "10 or more pyrimidine nucleotides of the sense strand and antisense strand are chemically modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides." New claim 39 is dependent on claim 18 and recites "1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 phosphorothioate internucleotide linkages." Literal support for the amendments to claim 18 and new claim 39 can be found, *inter alia*, at page 30, lines 2-7 of the instant application as filed, which reads:

> In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

Additional support for the amendments to claim 18 and new claim 39 can be found throughout the specification, including the Tables and Figures. For example the representative constructs described in **Table IV**, the hundreds of representative sequences that were designed and synthesized as shown in **Table I**, and which were tested for RNAi activity *in vitro* and *in vivo* as is shown in **Figures 10, 11, 12, 13, 14, 15, 26, 29, 30, 39, 40, 41, 77, 80, 81, 82, 83, 84, 85, 86, and 87,** all provide support for the instant claims. Additional examples can be found in **Figures 18 and 19**, demonstrating that the modifications or modification features as combined in the present claims were clearly contemplated as the invention at the time of filing. Moreover,

Figure 22 shows representative examples of terminal cap moieties.

Literal support for the amendments to claim 18 and new claim 39 can similarly be found in the following priority applications, all of which contain the language cited above and numerous representative examples and data.

PCT/US03/05346 filed February 20, 2003 contains the cited language at page 20, which reads:

> In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

Provisional application 60/408,378 filed September 5, 2002 contains the cited language at page 13, which reads:

> In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

Provisional application 60/358,580 filed February 20, 2002 contains the cited language at page 10, which reads:

> In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 pyrimidine nucleotides of the sense and/or antisense siRNA stand are chemically modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3', 5', or both 3' and 5'-ends, being present in the same or different strand.

The instant claims thus remain entitled to a priority date of February 20, 2002. Also, the

proposed amendments do not add new matter, and Applicants respectfully request their entry.

Double Patenting

Applicants thank the Examiner for withdrawing the previously asserted double-patenting rejections (except for the one directed to 10/923,536), in view of the arguments submitted on December 26, 2008.

Claims 18-20 and 33-38 remain provisionally rejected on the ground of non-statutory obviousness-type double patenting as allegedly being unpatentable over claims 33-50 of copending Application No. 10/923,536. Office Action, at pages 16-18. Without acquiescing to the Office's contentions, Applicants respectfully request that the Examiner hold these rejections in abeyance until such time when they become the sole remaining rejections in the instant application. Applicants then request that these rejections be withdrawn in accordance with MPEP § 804 I.B., which states:

> *If the "provisional" ODP rejections in two applications are the only rejections remaining in those applications, the examiner should then withdraw the ODP rejection in the earlier filed application thereby permitting that application to issue without need of a terminal disclaimer.*

Obviousness – 35 U.S.C. § 103(a)

Claims 18-20 and 33-38 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Elbashir (The EMBO J. 2001, Vol. 20 (23), 6877-6888), in view of Matulic-Adamic (US 5,998,203), Parrish (Molecular Cell, 2000, Vol. 6, 1077-1087), and Crooke (U.S. 5,898,031). Office Action, at page 3. Applicants respectfully traverse for the reasons below.

RESPONSE TO THE EXAMINER'S ARGUMENTS

The Examiner states that "it would have been prima facie obvious to perform routine optimization to determine which of the known modifications or combinations of modifications are optimal," and that "[r]outine optimization is not considered inventive and no evidence has been presented that the selection of the specific modifications used were other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any was as compared to the closest prior art." Office Action,

at pages 9-10. Applicants respectfully traverse, and maintain that the presently claimed invention cannot be obvious for at least two reasons. First, ***one of skill in the art would not have had any reasonable expectation of success in practicing the claimed invention at the time of the invention*** because the prior art either taught away from the claimed invention, or indicated a high level of unpredictability that would have precluded a reasonable expectation of success. Second, the Office is ***succumbing to impermissible hindsight*** in arguing that the present invention is obvious because it would be "obvious to try" the combinations of known modifications using "routine optimization," even though the prior art gave "no direction as to which of many possible choices is likely to be successful" and offered "only general guidance as to the particular form of the claimed invention or how to achieve it." *See In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)

1. ***Key references taught away from the claimed invention and suggested a high level of unpredictability***

The instant claims recite short nucleic acid duplexes having ***extensive modification*** with ***different types of modifications*** combined into each molecule, not only at ***specific positions*** but also on ***specific types*** of nucleotides. For example, instant claim 18 recites terminal caps at specific positions (both 3' and 5'-end positions of the sense strand only), plus extensive modification of specific nucleotides with specific modifications (10 or more 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro pyrimidine modifications in the sense and the antisense strands). Dependent claims 33, 34, 35, 36, and 37 recite further specific modifications of pyrimidine and purine nucleotides. Claim 39 recite the further inclusion of 1-10 phosphorothioate modifications.. Claim 19 recites a molecule that is 100% modified according to the limitations of claim 18.

The closest prior art is the Elbashir reference cited herein. Elbashir taught that molecules that were "more extensively" modified than beyond up to four 3'-terminal nucleotides "reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly." *See* Elbashir, at page 6885, under "The siRNA user guide." Elbashir based this teaching or suggestion on experimental results obtained from the following constructs (wherein squares represent purine nucleotides (A or G) and circles represent pyrimidine

nucleotides (U, C, or T); shaded regions represent 2'-deoxy nucleotides)):

CGUACGCGGAAUACUUCGAAA -3'
3'- GTGCAUGCGCCUUAUGAAGCU

CGUACGCGGAAUACUUCGAAA -3'
3'- GTGCAUGCGCCUUAUGAAGCU

Elbashir described the experimental results on pages 6881-6882, and in Figure 4, which are reproduced below:

2'-deoxy- and 2'-O-methyl-modified siRNA duplexes

To assess the importance of the siRNA ribose residues for RNAi, duplexes with 21 nt siRNAs and 2 nt 3' overhangs with 2'-deoxy- or 2'-*O*-methyl-modified strands were examined (Figure 4). Substitution of the 2 nt 3' overhangs by 2'-deoxynucleotides had no effect and even the replacement of two additional ribonucleotides by 2'-deoxyribonucleotides adjacent to the overhangs in the paired region produced significantly active siRNAs. Thus, 8 out of 42 nt of a siRNA duplex were replaced by DNA residues without loss of activity. Complete substitution of one or both siRNA strands by 2'-deoxy residues, however, abolished RNAi, as did complete substitution by 2'-*O*-methyl residues.

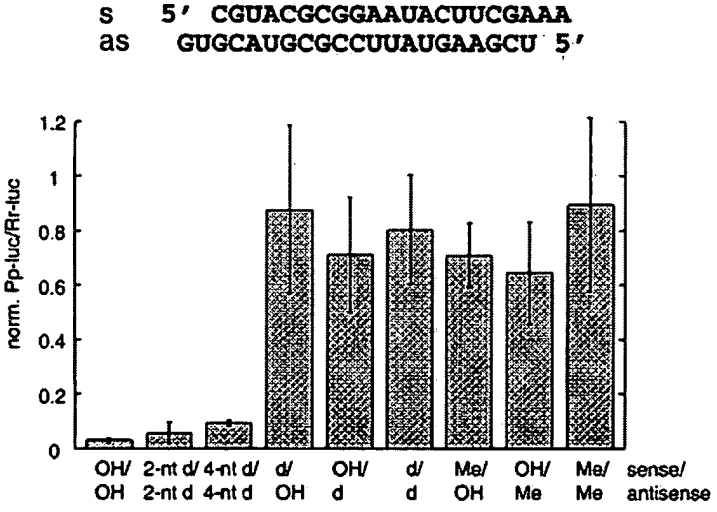

Fig. 4. Substitution of the 2′-hydroxyl groups of the siRNA ribose residues. The 2′-hydroxyl groups (OH) in the strands of siRNA duplexes

were replaced by 2′-deoxy (d) or 2′-*O*-methyl (Me). 2 and 4 nt 2′-deoxy substitutions at the 3′ ends are indicated as 2- and 4-nt d, respectively. Uridine residues were replaced by 2′-deoxythymidine.

From these data, Elbashir expressly taught away from "more extensive modifications," as evidenced in the paragraph below reproduced from "The siRNA user guide:"

> ***The siRNA user guide***
>
> Efficiently silencing siRNA duplexes are composed of 21 nt sense and 21 nt antisense siRNAs and must be selected to form a 19 bp double helix with 2 nt 3'-overhanging ends. 2'-deoxy substitutions of the 2 nt 3'-overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNase resistance of siRNA duplexes. ***More extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly.***

Therefore, the simple fact that the instant Applicants taught and claimed "more extensively" modified nucleic acid duplexes, i.e., molecules that are extensively and differentially modified beyond up to four 3'-terminal nucleotides and with more than a single type of modification (2'-deoxy), and which have demonstrated robust RNAi activity both *in vitro* and *in vivo* (*see* experimental results, such as those represented in Figures 10, 11, 12, 13, 14, 15, 26, 29, 30, 39, 40, 41, 77, 80, 81, 82, 83, 84, 85, 86, and 87 of the instant application), should indicate an unobvious invention achieved by following a path taught away by the prior art.

In this regard, the position taken by the Office that "Elbashir et al. are considered to offer motivation to incorporate chemical modifications at various percentages to optimize the activity of the duplex because not all modifications result in activity at every percentage" (Office Action, at page 11) cannot be reconciled with the clear warning against "more extensive modifications" in a "user guide" published by a leading group of researchers who pioneered early characterization of siRNAs. It is respectfully submitted that the Office appears to be picking and choosing portions while ignoring other parts of the references rather than looking at them as a whole. But this practice does not comport with a proper determination of obviousness, which requires that the prior art reference be considered in its entirety as a whole including portions that lead away from the claimed invention. MPEP § 2141.02, citing *W.L.Gore & Assoc. Inc. v.*

Garlock, Inc., 721 F.2d 1540 (Fed. Cir. 1983). Where an insight of an inventor is contrary to the understanding and expectations of the art, a structure effectuating it would not have been obvious. *Schenck v. Nortron Corp.*, 713 F.2d 283, 785 (Fed. Cir.1983). The Supreme Court in *KSR* emphasized the key importance of a teaching away reference, stating that, "[w]hen the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *KSR Int'l Co.* 127 S. Ct. 1727, 1740 (2007 (citing *United States v. Adams*, 383 U.S. 39, 51-52 (1966)). Proceeding when there is a teaching away supports nonobviousness, not motivation. *See also*, MPEP §2145 ("proceeding contrary to accepted wisdom is evidence of nonobviousness").

Indeed, the Office erroneously concluded that "Elbashir is evidence that modification is well tolerated in the terminal portions of the duplex, offering further motivation to modify the terminal regions." Office Action, at page 12. Correctly read, Elbashir in no way suggests modifying ***both*** terminal regions of a given strand, be it a sense strand or an antisense strand. In fact, Elbashir succeeded in only modifying a single terminal region, i.e., the 3'-end; with a single type of modification, i.e., 2'-deoxy; and to a limited extent, i.e., up to 4 nucleotides at the 3'-terminus. In all instances where other modifications other than limited 2'-deoxy substitutions at the 3'-terminus were used, including all instances where the 5'-terminus were modified, activity was "abolished." Extension of Elbashir's limited findings to other nucleotide modifications (e.g., 2'-O-methyl) and other positions within the siRNA (e.g., beyond the four 3'-terminal nucleotides) is therefore improper on its face and is an indication of hindsight analysis.

Parrish, the only other RNAi-related references cited by the Office, disclosed certain chemical modifications, such as 2'-deoxy-2'-fluoro uridines, as compatible with RNAi activity in a long double stranded RNA (*unc-22,* which is 742 nt-long). There was no suggestion by Parrish that 2'-deoxy-2'-fluoro could be applied, with sustained RNAi activity, to other types of nucleotides (e.g., cytidines), or to short RNA duplexes. Importantly, Parrish taught away from incorporating 2'-deoxy modifications (as are presently claimed) because they were found to be detrimental to RNAi activity, a point that was entirely ignored by the Office. Specifically, Parrish described that modification of cytidine to deoxycytidine (or uracil to thymidine) on either the sense or the antisense strand produced substantial decrease in interference activity. *See* Parrish, at page 1081, right column. Parrish also taught away from applying more than one phosphorothioate modification to different nucleotide bases because more than one

phosphorothioate base modification greatly reduced RNAi activity, and more than two phosphorothioate base modifications abolished RNAi activity. *See* Parrish, at page 1084. Moreover, Parrish repeatedly stated that activity was more sensitive to modification of the antisense strand than modification of the sense strand. *See* Parrish, at page 1081, 1082 & 1084. Therefore, the fact that the instant Applicants taught and claimed extensively modified nucleic acid duplexes, modified with ***2'-deoxy*** and ***phosphorothioate*** modifications to multiple types of nucleotide bases ***on both the sense and the antisense strands***, and which have demonstrated robust RNAi activity (see experimental results such as those represented in Figures 10, 11, 12, 13, 14, 15, 26, 29, 30, 39, 40, 41, 77, 80, 81, 82, 83, 84, 85, 86, and 87 of the instant application), should be yet another indication that an unobvious invention was achieved by following a path taught away by Parrish.

In fact, the cited references provided clear evidence that it ***was highly unpredictable*** at the time of the present invention as to whether and how the chemical modifications that had been developed for antisense and ribozyme fields might be applicable to siRNA molecules without abrogating RNAi activity. Specifically, it must first be noted that the Office misread Matulic-Adamic as teaching or directing those skilled in the art to modify, with the terminal cap moieties, a ***double-stranded*** nucleic acid structure as claimed herein. The nucleic acid molecules of Matulic-Adamic are all ***single-stranded*** ribozyme oligonucleotides that have secondary structures, such as stem loop regions. These stem loop regions are the only possible basis for double-stranded structures being disclosed in Matulic-Adamic. However, none of these secondary structures have more than 5-base pairs; none have complementarity to a target RNA; and none have terminal cap moieties at the 3' and 5'-ends. In fact, inclusion of the instantly claimed features in the stem loop regions of the Matulic-Adamic ribozymes would be physically impossible, as these stem loop regions are secondary structures that arose from folding a ***single strand***. Therefore, any guidance as to predictability with respect to the terminal caps and other chemical modification strategies taught by Matulic-Adamic is limited to use in single-stranded ribozymes to support ribozyme catalysis. Likewise, it should be noted that Crooke's teaching of chemical modifications were limited to antisense gapmers, which are also clearly single-stranded constructs. Nowhere in Crooke was there any mention that the chemical modifications described therein can be suitable or beneficial for molecules other than single-stranded gapmers that have,

when base-paired to a target mRNA, become RNAse H substrates. Therefore, unless there was teaching in the art to indicate that modifications previously known to be applicable to a single-stranded ribozyme (such as those in Matulic-Adamic), or a single-stranded antisense nucleotide (such as those in Crooke) can be ***predictably*** applied to a double-stranded siRNA molecule without abrogating RNAi activity, the skilled person in the art was faced with no reasonable expectation of success in applying any of the stabilizing modifications disclosed in Matulic-Adamic or Crooke to an siRNA molecule, let alone in using of such modifications both extensively and differentially in combination.

The closest prior art, Elbashir, taught only limited modification of the 3'-terminal overhangs with a single type of modification, and warned against "more extensive modifications." While generically suggesting the use of 2'-deoxy modification (to stabilize the 3'-overhangs of an siRNA molecule), Elbashir was unequivocal in stating that "[c]omplete substitution of one or both siRNA strands by 2'-deoxy residues, however ***abolished*** RNAi, as did substitution by 2'-O-methyl residues." *See* Elbashir, at page 6882. Elbashir also expressly stated that, while 2'-deoxy substitution of the 3'-overhang ribonucleotides does not affect RNAi, "[m]ore extensive 2'-deoxy or 2'-O-methyl modifications, however, reduce the ability of siRNAs to mediate RNAi." *See* Elbashir, at page 6885. It would not have escaped the notice of a skilled person in the art that all of the Elbashir modifications that could lead to abolished RNAi activity if applied too much or at the wrong positions, i.e., 2'-deoxy and 2'-O-methyl used either in internal positions or 5'-terminal positions, were those found to be generically "beneficial" to the other single-stranded molecules. For example, 2'-fluoro and 2'-O-methyl modifications were found to benefit the Crooke gapmers; and 2'-deoxy, 2'-fluoro, and 2'-O-methyl modifications were found to benefit the Matulic-Adamic ribozymes.

Parrish suggested the same lack of predictability. Indeed, it repeatedly taught that RNAi activity was more sensitive to modification of the antisense strand than modification of the sense strand, and that depending on the type and location of the modification, inactivity would result. *See* Parrish, at pages 1081, 1082 & 1084. Therefore Parrish confirmed that the use of known modifications from other nucleotide arts, such as antisense and ribozyme applications, led to unpredictable results in RNAi applications at the time of its publication. Moreover, as discussed at length above, Parrish effectively taught away from using 2'-deoxy modification and

phosphorothioate modifications, as presently claimed, even though these modifications were found to be generically beneficial to the gapmers of Crooke and to the ribozymes of Matulic-Adamic. Thus, known modifications that were applicable and/or beneficial to single-stranded antisense molecules (such as 2'-fluoro and 2'-O-methyl modifications, according to Crooke), and to single-stranded ribozymes (such as 2'-deoxy, 2'-fluoro, and 2'-O-methyl modifications, according to Matulic-Adamic) were often found to be detrimental to double-stranded RNA molecules. In fact, in all instances but one (i.e., 2'-deoxy modifications on 3'-overhang plus two immediately adjacent nucleotides), the beneficial effect of improved stability was severely tempered by the loss of RNAi activity. In this regard, the present invention drawn to extensively and differentially modified short double-stranded nucleic acid molecules having robust RNAi activity does indeed provide surprising and an unexpected result in view of the state of the art at the time. Therefore, a person skilled in the art at the time of the present invention was faced with a complete lack of predictability and no reasonable expectation of success to apply modifications developed for the antisense and ribozyme applications to an siRNA as presently claimed.

2. ***"Obvious to try" analysis under In re Kubin in view of In re O'Farrell also precludes a finding of obviousness***

In supporting a finding of obviousness, the Office takes the position that "one would have a reasonable expectation of success given that each of the modifications were known in the art at the time the invention was made to add benefits to antisense oligonucleotides, ribozymes or siRNA duplexes" and that "[i]t would have been prima facie obvious to perform routine optimization to determine which of the known modification or combinations of modifications are optimal," Office Action, at pages 9-10. At the outset, it should be noted that Applicants are not claiming the method of applying modifications to siRNA using "routine optimization."

The Office is essentially arguing that the present invention would be "obvious to try" using known modifications and routine experimentation. Applicants respectfully disagree.

First, a representative sequence from **Figure 19C** of the instant application, which meets the instant claim limitations of extensive and differential modification is pictured below: squares represent purine nucleotides (A or G) and circles represent pyrimidine nucleotides (U, C, or T);

shaded regions represent 2'-deoxy (T) and 2'-deoxy-2'-fluoro (U, C) nucleotides; S represents phosphorothioate; and iB represents cap moieties on the 3' and 5'-ends of the sense strand.

Moreover, another representative sequence from **Figure 19E** of the instant application meeting the extensive and differential modification limitations is pictured below: squares represent purine nucleotides (A or G) and circles represent pyrimidine nucleotides (U, C, or T); shaded circles represent 2'-deoxy (T) and 2'-deoxy-2'-fluoro (U, C) nucleotides; shaded squares represent 2'-O-methyl (G, A) in the antisense strand and 2'-deoxy (G, A) in the sense strand; S represents phosphorothioate; and iB represents cap moieties on the 3' and 5'-ends of the sense strand. This construct is 100% modified.

For comparison, the modified siRNA molecules with retained RNAi activity from Figure 4 of the closest prior art, Elbashir et al. is pictured below: squares represent purine nucleotides (A or G) and circles represent pyrimidine nucleotides (U, C, or T); shaded regions represent 2'-deoxy nucleotides:

From these pictures alone, it can hardly be said that the claimed molecules can be derived from routine optimization of the even the closest prior art molecules.

The Federal Circuit recently clarified the standard for finding obviousness based on "obvious to try" in *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009). While acknowledging that, as stated by the U.S. Supreme Court in *KSR International Co. v Teleflex Inc.*, a skilled

artisan, when motivated by an unmet need, can look to combine elements within the scope of the prior art, it would be improper to hold a claim obvious when:

> what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result; where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful

or

> what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

To hold a claim obvious under these situations would be, according to the Federal Circuit, "succumb[ing] to hindsight claims of obviousness" and erroneous. *Id.* Reaffirming its prior holdings in *In re O'Farrell,* 853 F.2d 894, 903 (Fed. Cir. 1988), the Federal Circuit explained that in order for an "obvious to try" situation to serve as the basis for obviousness, some direction in the prior art that would provide a reasonable expectation of success is still required. *See, O'Farrell,* at 903-04.

It should first be noted that the instant claims are drawn to molecules that combine different types of modifications: i.e. 3'- and 5'-terminal cap moieties and 10 or more 2'-deoxy, 2'-fluoro, or 2'-O-methyl modified pyrimidine nucleotides in the sense and antisense strands. There is nothing in the cited references that could have been taken to suggest a combined application of 5'- and 3-terminal cap moieties of the sense strand with 10 or more 2'-modified pyrimidines in the sense and antisense strands in an siRNA context. As explained above, the Crooke reference is drawn to an antisense gapmer, and all of the modifications disclosed therein, ***which do not include terminal cap moieties,*** were specifically developed for antisense molecules to recruit RNAase H when base paired to an RNA. Matulic-Adamic is drawn to a hammerhead ribozyme, and all of the modifications disclosed therein were specifically developed to improve stability of the largely single-stranded construct while supporting the catalytic activity of the ribozyme. There was no indication whatsoever from either Crooke or Matulic-Adamic that these modifications could be applied to a short nucleic acid duplex without abrogating RNAi activity. Elbashir does not teach or suggest the combination of modifications from ribozyme and

antisense art. In fact, each of the chemically modified Elbashir siRNA molecules, ***active or not,*** contained a single type of modification. It was either a 2'-deoxy, or a 2'-O-methyl. None of the molecules in that reference contained or even contemplated a terminal cap moiety, let alone putting a terminal cap moiety on both ends of the sense strand, in addition to 10 or more 2'-deoxy, 2'-fluoro, or 2'-O-methyl modified pyrimidine nucleotides in the sense and antisense strands. Likewise, Parrish did not teach molecules that were modified with more than a single type of modification. All of the modified molecules in that reference, ***active or not,*** contained a single type of modification. Again, a terminal cap moiety was not even contemplated. Therefore, the prior art did not provide or indicate any direction as to which of the many possible choices would likely lead to success.

Indeed, the number of possibilities for the modifications taught by the prior art is very large, and the number and types modifications to an siRNA is nearly infinite when one factors into consideration that the claims also require specific combinations of modifications and specific modification at certain positions or certain types of nucleotides in the duplex. Not only did the references cited herein provide no guidance as to what combinations of modifications when used extensively can result in siRNA molecules that are both active and stable, they in fact indicated that extensive incorporation of modifications into an siRNA was in fact detrimental, or at least highly unpredictable. Thus, to arrive at the presently claimed invention would clearly require extensive combination and testing of these modifications, among others that had also been disclosed, even though these modifications were taught by the cited references to be often detrimental when applied "more extensively." Therefore, even an "obvious to try" inquiry fails to result in a finding of obviousness as one of skill in the art would simply have ***no reasonable expectation of success*** in practicing the instantly claimed invention.

Finally, even if one takes the position that routine testing with known modifications and known assays would ***eventually*** lead one of skill in the art to the presently claimed invention, this would be insufficient to establish a *prima facie* case of obviousness for at least two reasons. First, the references cited by the Office fails to give any indication of which parameters were critical to success, and in many instances taught away from the claimed modifications. Second, at the time of the present invention, RNAi was a new technology and the experiences of the antisense/ribozyme arts at most gave general guidance as to types of modifications one could

apply to an siRNA molecule, providing merely a large toolbox of possibilities. But these known modifications were individually demonstrated by those who first studied siRNAs in the field to be sometimes feasible, but more often than not incompatible with RNAi activity. That unpredictability grows only larger if the known modifications were applied extensively, up to 100%, and in combination. Thus, although numerous types of modifications were known in the art, this was not a case of testing a finite number of identified, predictable solutions. "In such circumstances, where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness." *Kubin,* at 1359.

Therefore, this is not an instance where the prior art "contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, ***and evidence suggesting that it would be successful.***" Rather, it is an instance where the prior art provides "no direction as to which of many possible choices is likely to be successful" and "only general guidance as to the particular form of the claimed invention or how to achieve it." Most importantly, the prior art, by teaching that either (1) more extensive modification, or (2) differential modification, is detrimental (in all instances examined), evidenced such a high level of unpredictability to preclude any reasonable expectation of success in practicing the claimed invention, which calls for both (1) more extensive modification and (2) differential modification. Applicant's arguments do not rest on an absolute predictability of success, but rather point to a fundamental lacking of even a reasonable expectation of success. Any finding of obviousness under the "obvious to try" standard is therefore improper under the jurisprudence of *Kubin* and *O'Farrell.*

Thus, the pending claims are not *prima facie* obvious over the cited references and Applicants respectfully request withdrawal of the obviousness rejections.

Conclusion

In view of the foregoing, Applicants respectfully submit the pending claims are in condition for allowance but for the residual provisional double-patenting issues. If the Examiner believes a

telephone conference would expedite prosecution of this application, she is urged to telephone the undersigned at the telephone number below.

Respectfully submitted,
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Date: July 21, 2009

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